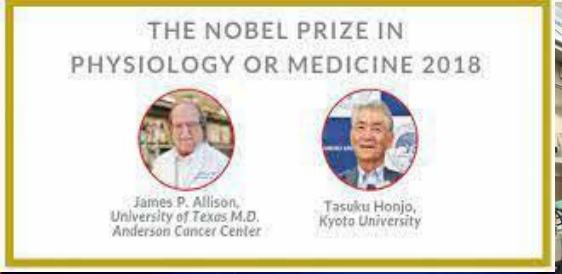
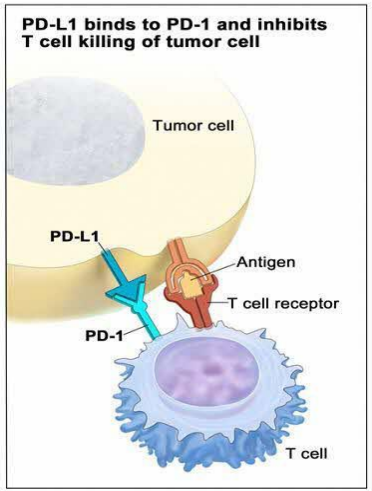
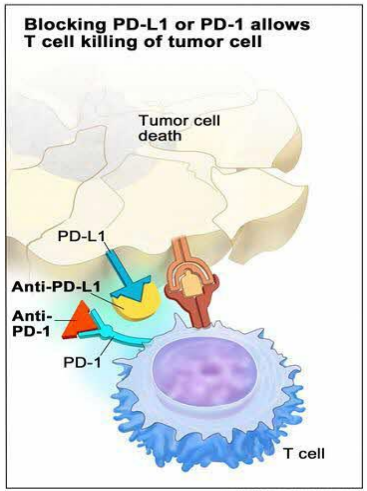
HARNESSING IMMUNE CELLS : CAN IT TREAT EVERY CANCER EVERYWHERE ALL AT ONCE ?

TOH HAN CHONG
Deputy CEO
National Cancer Centre Singapore
Professor
Duke NUS Medical School

T CELLS AS LIVING THERAPY

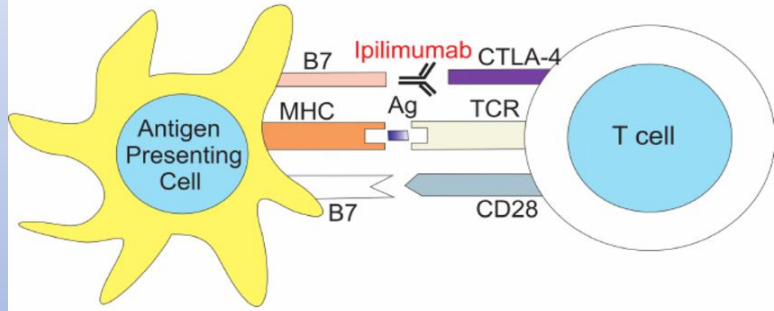






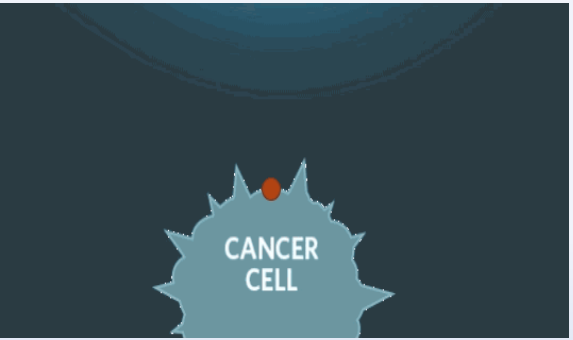
2011 : THE ARRIVAL AND APPROVAL OF THE FIRST LARGE SCALE IMMUNOTHERAPY – IMMUNE CHECKPOINT INHIBITOR ANTIBODIES

CTLA-4, inhibitory receptor blocks T cell activation. Ipilimumab blocks CTLA-4 and augments T cell activation



B7, co-stimulatory "ligand" activates co-stimulatory receptor Cd28 and stimulates T cell

2017 : ARRIVAL OF CAR T CELL THERAPY – A REMARKABLE BREAKTHROUGH



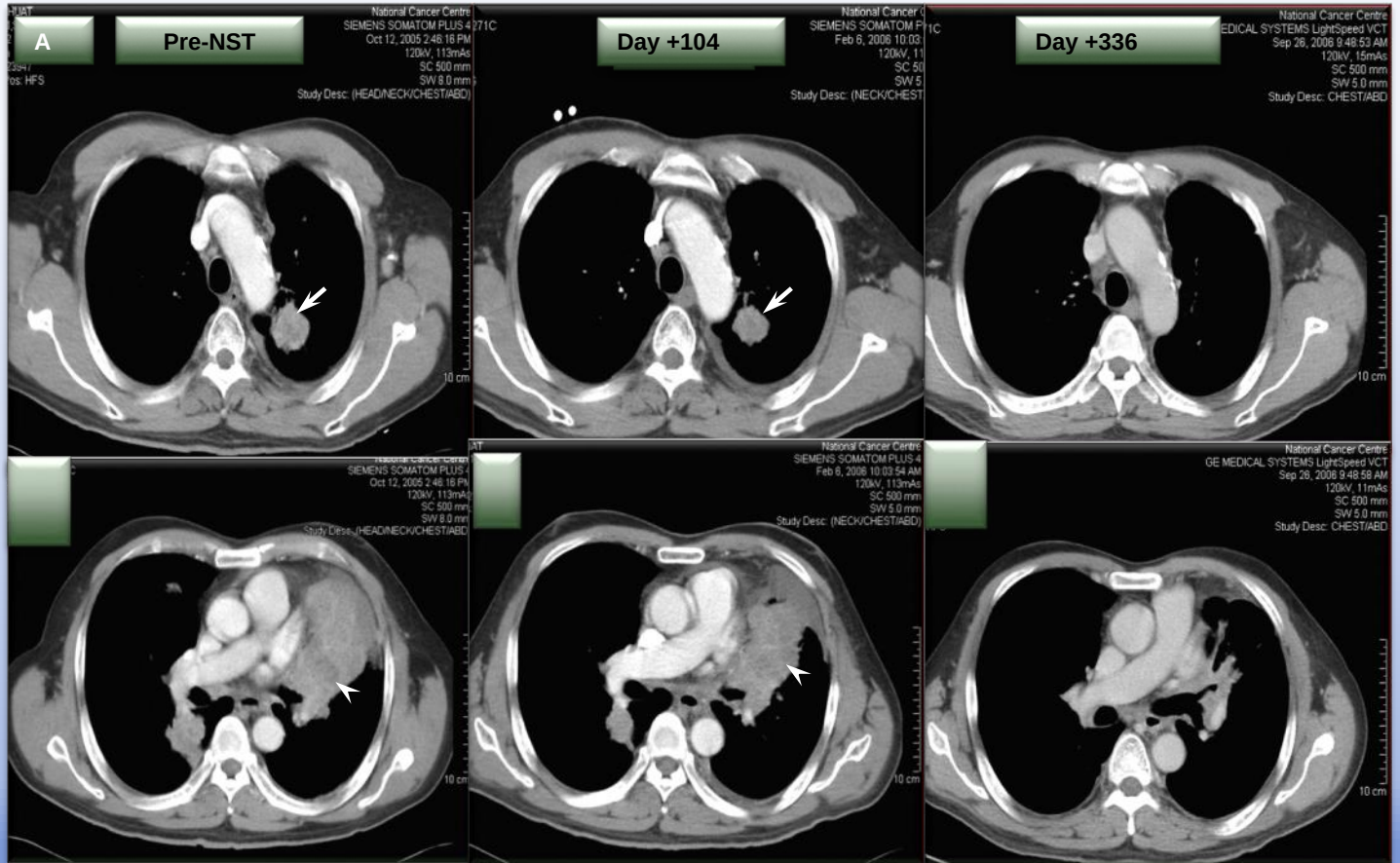
GIVING ALLOGENEIC BLOOD STEM CELLS TO PATIENTS WITH CANCER – AN EARLY SIGNAL OF AN IMMUNE RESPONSE AGAINST CANCER

Nonablative preparative regimen to achieve engraftment → allo PBPC or BMT → short-time GvHD-prophy-laxis → DLI if residual disease

Achieve mixed chimaera

Achieve full donor chimaera

NPC MINITRANSPLANT : CT scan images for patient 16 at dy-13 (pre-NST), dy+104 and dy+336



FIRST DEMONSTRATION OF GRAFT-VS-NPC EFFECT

n = 21

33% PR

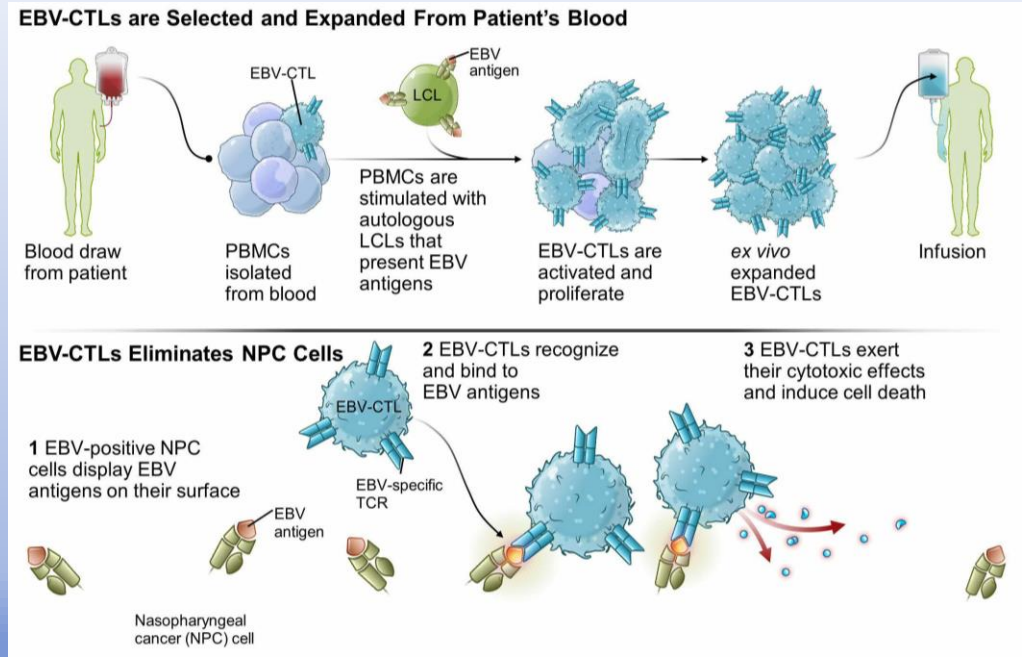
14% SD

Median PFS 100 days

Longest disease control 550 days

Toh HC et al. Bone Marrow Transplant April 2011

Epstein Barr Virus-Specific Autologous Cytotoxic Lymphocytes (EBV-CTL)



- NPC and EBV are strongly associated[1,2]
- EBV-CTL is an autologous adoptive T-cell immunotherapy generated from patient's blood & manufactured without genetic modification
- EBV-CTLs target antigens expressed in EBV (i.e., EBNA-1, LMP-1, and -2)
- Clinical proof of concept successfully demonstrated in four Phase 1/2 trials[3-6]
  - EBV-CTL therapy with standard first line treatment for NPC – feasible and well tolerated
  - Autologous EBV-CTL therapy demonstrates clinical benefit in patients with advanced EBV-associated NPC

DEVELOPMENT OF EBV VIRUS-SPECIFIC T CELLS AGAINST SOLID TUMOUR – NASOPHARYNGEAL CANCER

Baylor College of Medicine

National Cancer Centre Singapore
SingHealth

TESSA THERAPEUTICS

1990s

- Dr. Malcolm Brenner started studying body's natural anti-viral immune response to target cancer

2002-2007

- **Phase I** trials for patients with advanced nasopharyngeal cancer (NPC) conducted at Baylor College of Medicine

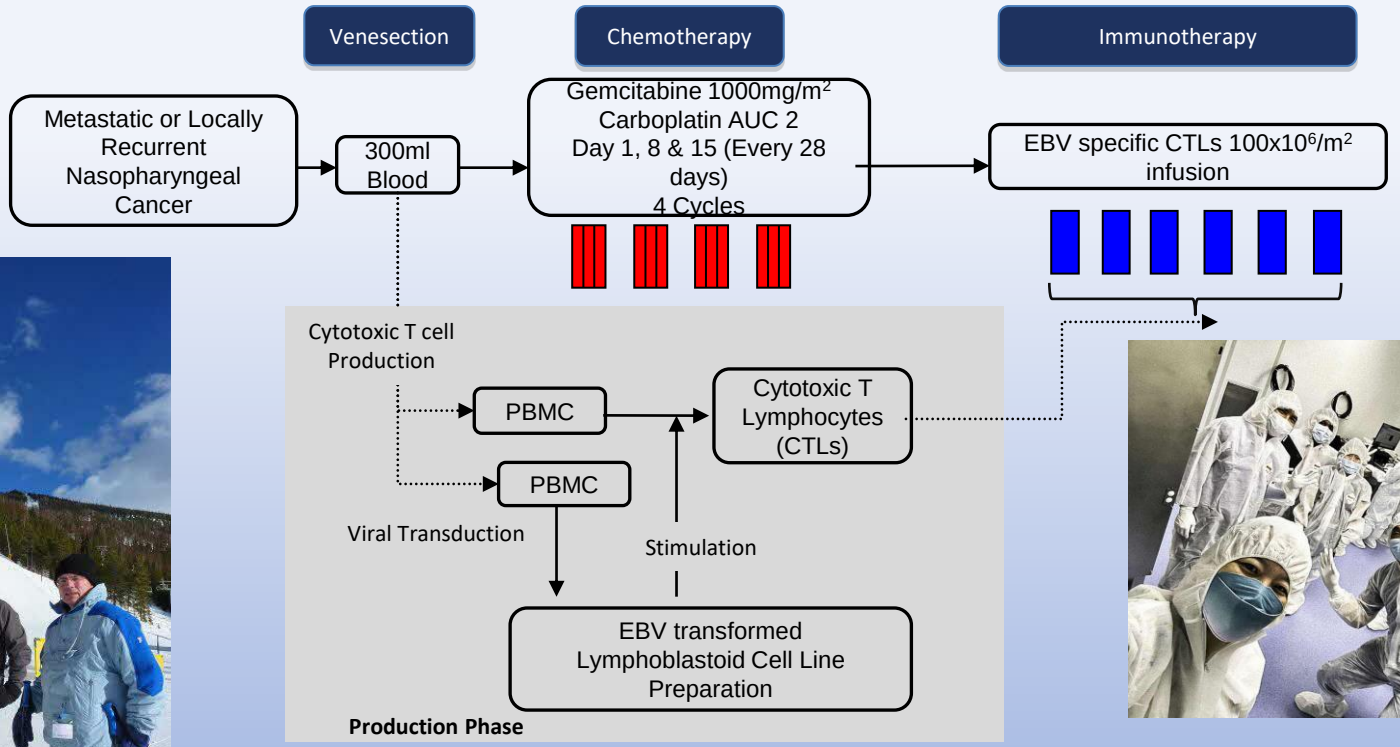
2008-2011

- **Phase II** trial at NCCS demonstrated then best 2-year survival data in patients with advanced NPC

2012-2014

- Tessa founded
- Commencement of **Tessa's Phase III** trial recruiting 330 patients across 30 hospitals in 5 countries – now completed

COMBINATION CHEMOTHERAPY & EBV CTL THERAPY IN ADVANCED NPC

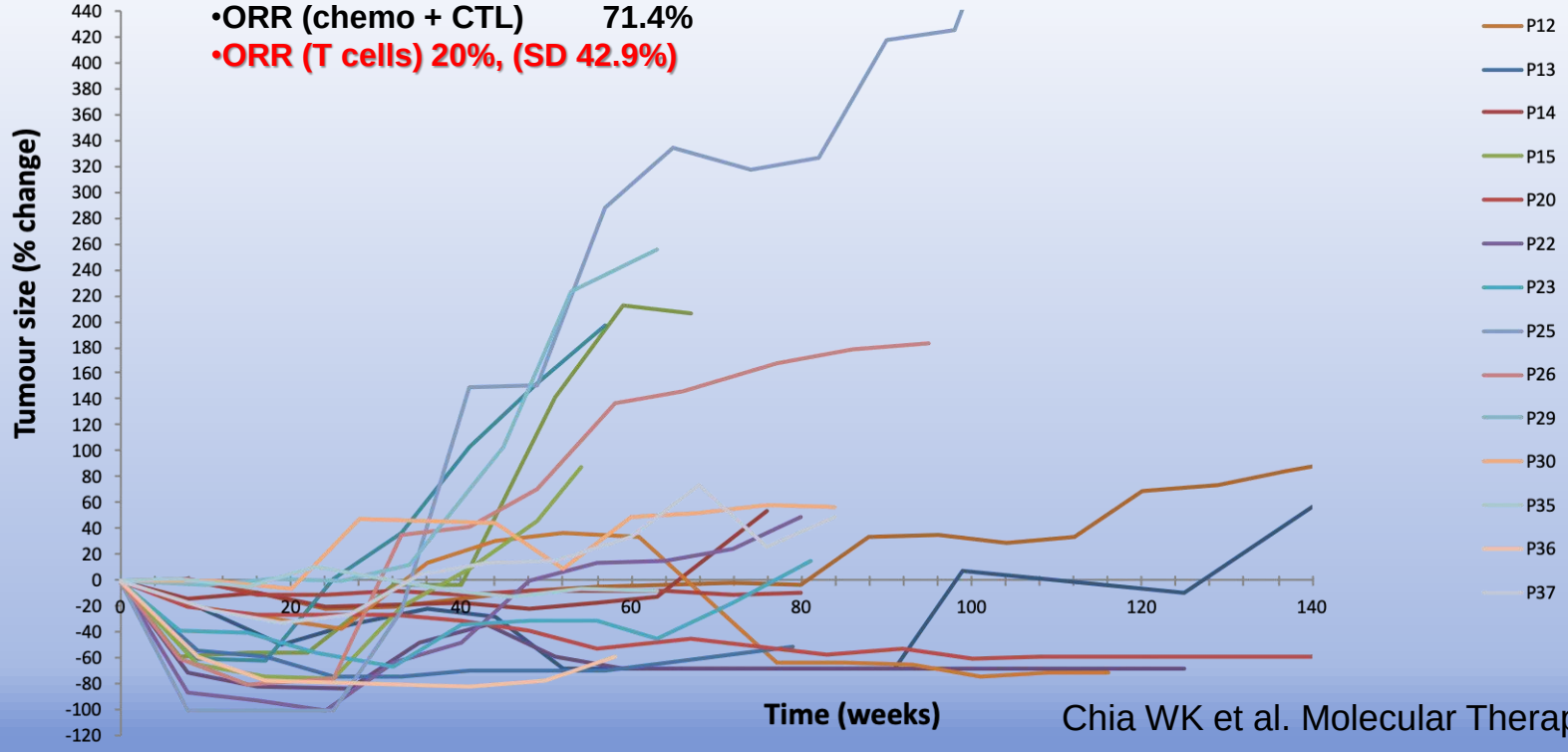


Chia WK et al. Molecular Therapy 2014

First Line Gemcitabine/Carboplatin & EBV CTL therapy

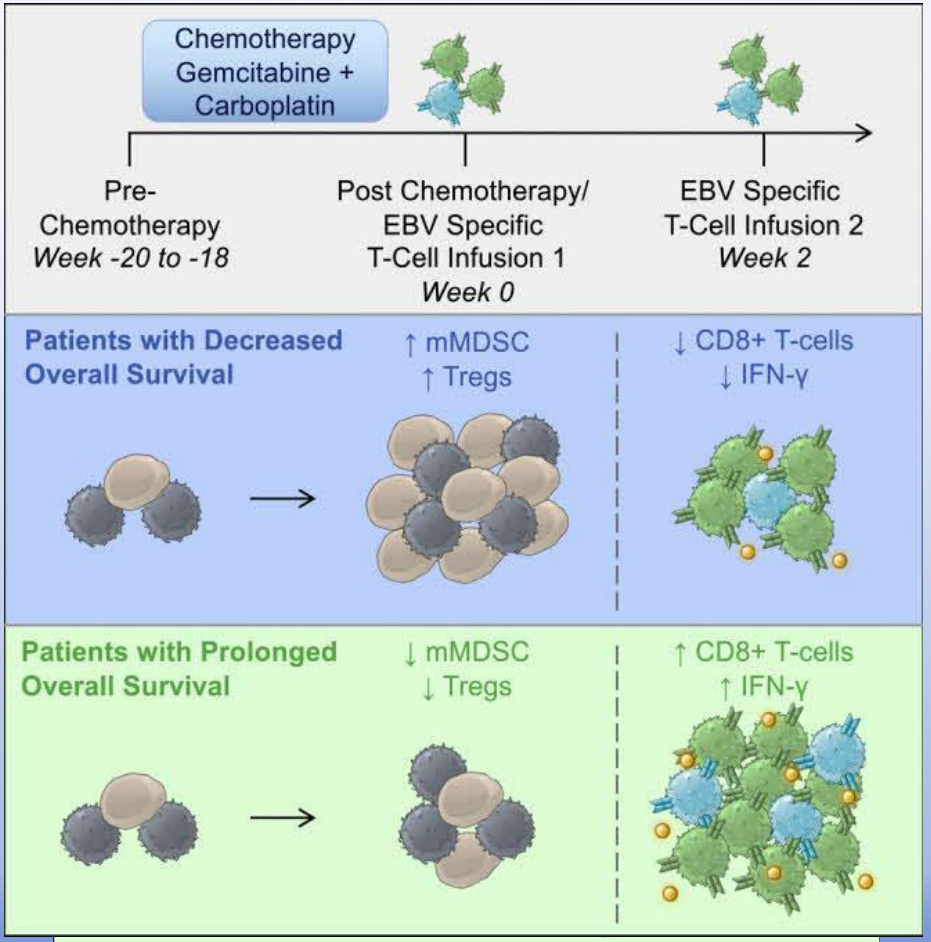
SPIDER PLOT OF TUMOUR SIZES

THESE ROLLERCOASTER LINES WERE NOT PREVIOUSLY SEEN WITH CHEMOTHERAPY

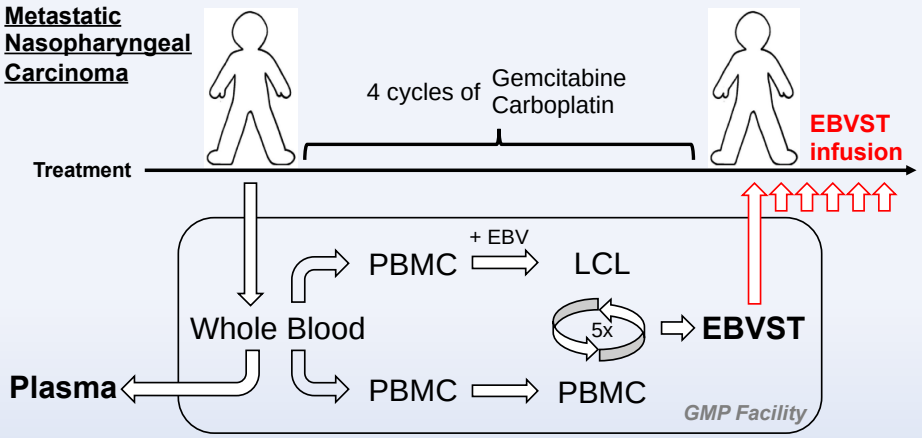


Chia WK et al. Molecular Therapy 2014

Monocytic Myeloid-Derived Suppressor Cells Underpin Resistance to Adoptive T Cell Therapy in NPC

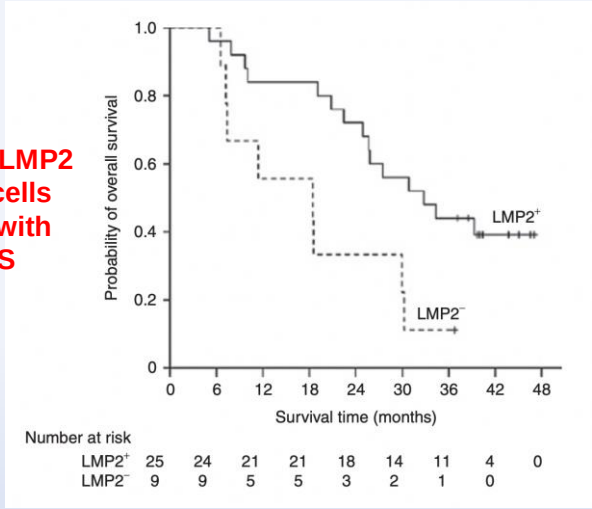


Hopkins R et al Molecular Therapy 2020



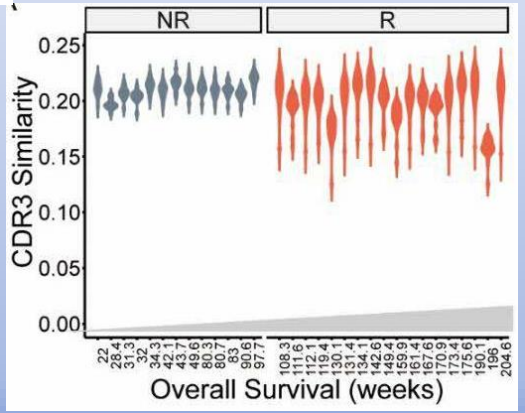
The 2-year and 3-year overall survival (OS) rate was 62.9 and 37.1%, respectively.

Presence of LMP2 specific T cells correlates with better OS



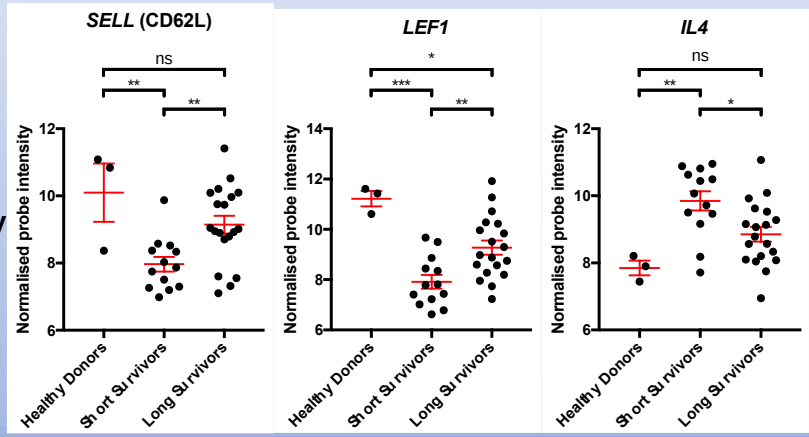
Chia et al 2014 *Molecular Therapy*

Higher diversity of TCR repertoires found in long-term survivors



Wang *et al* 2021 *OncoImmunology*

Prelim microarray analysis showing higher central memory related gene expression in long-term survivors



Shuen T *et al* unpublished

PARIS 2022 ESMO congress

Randomized Phase III VANCE Study: Gemcitabine and Carboplatin Followed by Epstein Barr Virus-specific Autologous Cytotoxic T Lymphocytes (EBV-CTL) Versus the Same Chemotherapy as First Line Treatment for Advanced Nasopharyngeal Carcinoma (NPC)

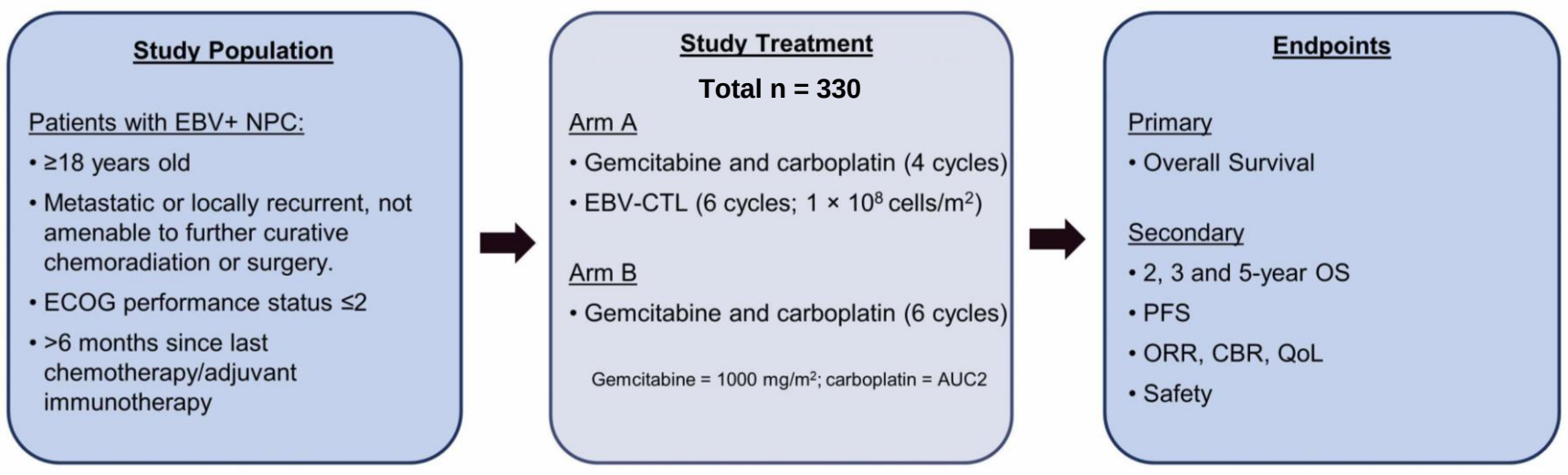
Han Chong Toh, Muh-Hwa Yang, Hung-Ming Wang, Ching-Yun Hsieh, Imjai Chitapanarux, Kean Fatt Ho, Ruey-Long Hong, Mei-Kim Ang, A. Dimitrios Colevas, Ekaphop Sirachainan, Chawalit Lertbutsayanukul, Gwo Fuang Ho, Jens Samol, Zhenbiao Huang, Clare Tan, Cliff Ding, Aung Myo on behalf of the VANCE trial Investigators.

Dr. Han Chong Toh
National Cancer Centre Singapore

VANCE Trial

World's largest clinical trial of adoptive T cell therapy in solid tumours reported

Multicenter, randomized, open-label, Phase III clinical trial

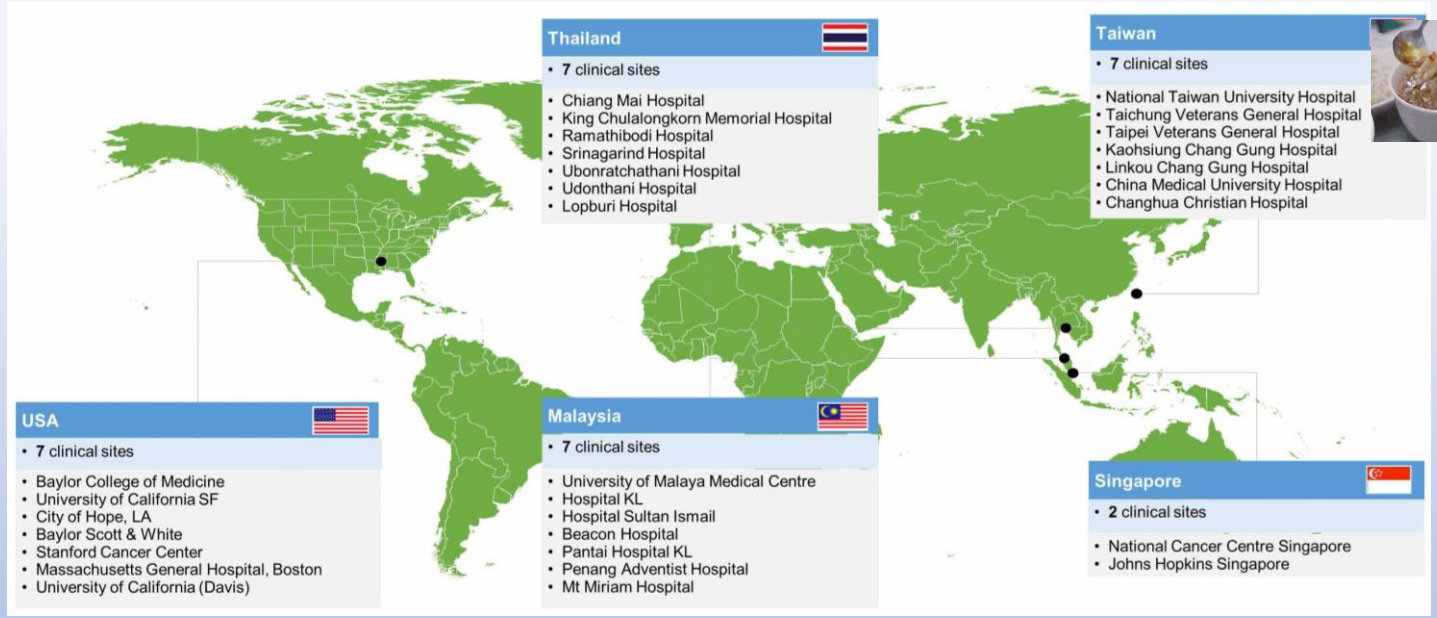


- Evaluated the efficacy of gemcitabine and carboplatin followed by EBV-CTL versus gemcitabine and carboplatin alone as first line treatment for locally recurrent but incurable and metastatic NPC
- Subjects allocated in 1:1 ratio

*EBV-CTL: 2 cycles every 2 weeks, followed by 4 cycles every 8 weeks after 6 weeks from second cycle

Abbreviations: AUC2, target area under the curve of 2 mg/mL × min; CBR, Clinical Benefit Rate; EBV, Epstein-Barr virus; EBV-CTL, Epstein Barr Virus-Specific Autologous Cytotoxic T Lymphocytes; ECOG, Eastern Cooperative Oncology Group; NPC, nasopharyngeal carcinoma; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; QoL, quality of life

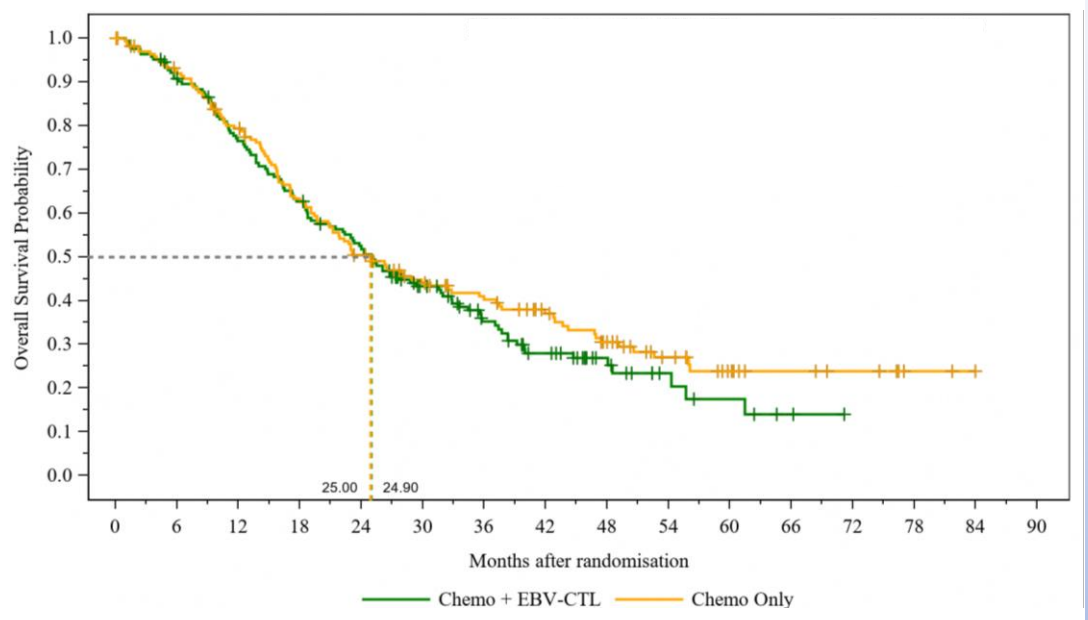
Setting up this global multicentre trial was a massive white hair inducing and yet rewarding experience



Autologous T Cell Therapy:The Central GMP facility was able to produce sufficient EBV-CTL for 94% of Arm A patients. Over 3,000 successful shipments through 79 shipment lanes across 5 countries / regions globally.

Overall Survival

No significant difference in OS between treatment arms



Median OS (months; 95% CI)

Chemo + EBV-CTL: 25.0 (19.7, 31.8)

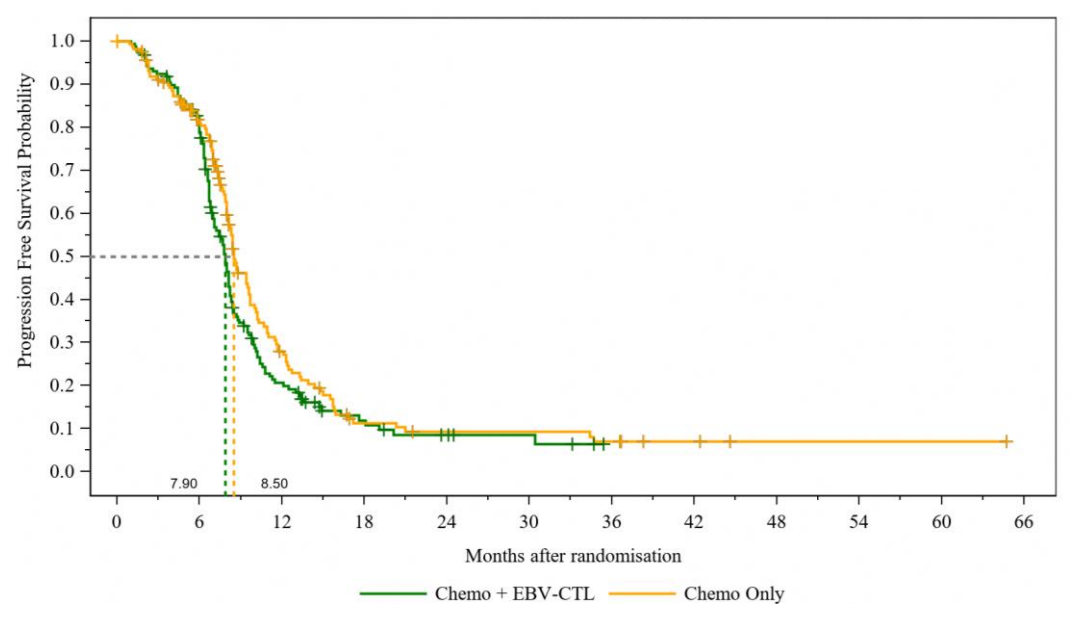
Chemo Only: 24.9 (19.7, 32.8)

Hazard ratio (95% CI): 1.19 (0.91, 1.56)

p = 0.1942

Abbreviations: CI, confidence interval; EBV-CTL, Epstein Barr Virus-Specific Autologous Cytotoxic T Lymphocytes; OS, overall survival

Progression-free Survival (PFS)



Median PFS (months; 95% CI)

Chemo + EBV-CTL: 7.9 (7.1-8.2)

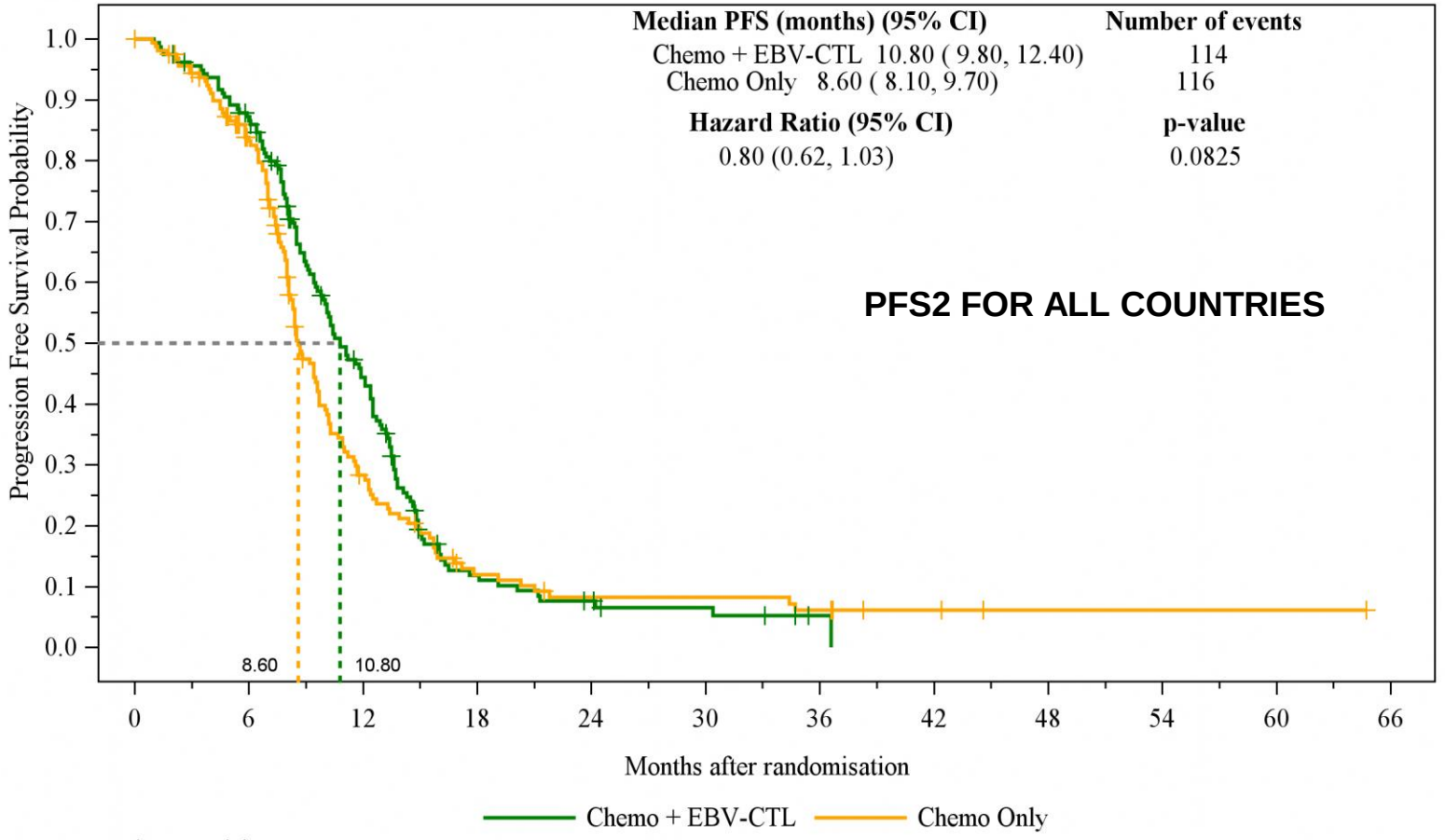
Chemo Only: 8.5 (8.1-9.6)

Hazard ratio (95% CI): 1.32 (1.02, 1.70)

p = 0.0370

Abbreviations: CI, confidence interval; EBV-CTL, Epstein Barr Virus-Specific Autologous Cytotoxic T Lymphocytes; PFS, progression-free survival

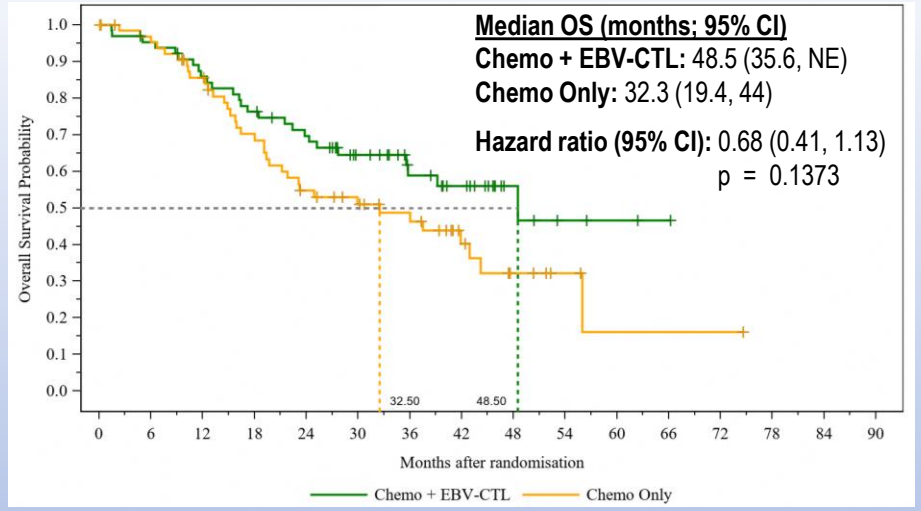
Figure 5.4 PFS: Kaplan-Meier Plot Progression Free Survival (PFS2) - Intent to Treat Analysis Set



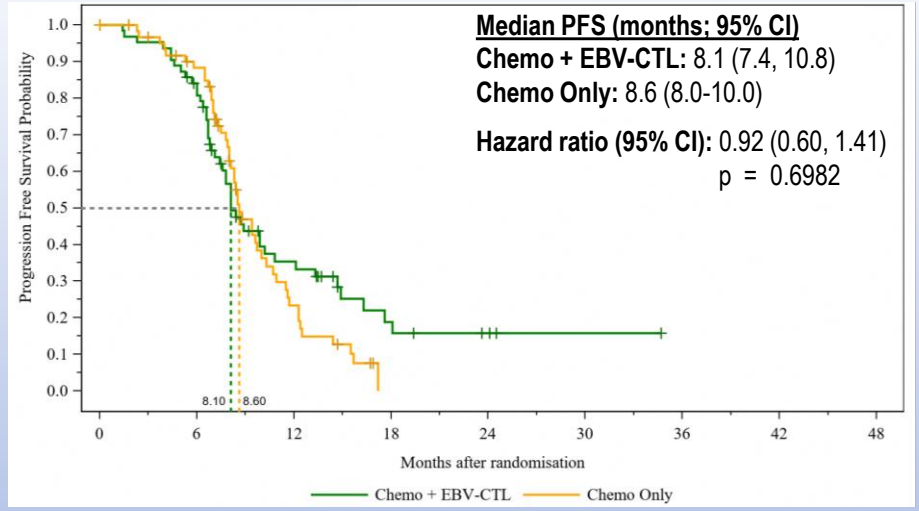
Patients at risk												
Chemo + EBV-CTL	164	134	62	14	8	5	1	0				
Chemo Only	166	122	36	13	8	8	6	3	1	1	1	0

Subgroup analysis of Overall Survival & Progression-free Survival 1 (PFS-1)

OS and PFS-1 of 3 countries / regions combined: US,Taiwan, Singapore



Overall Survival

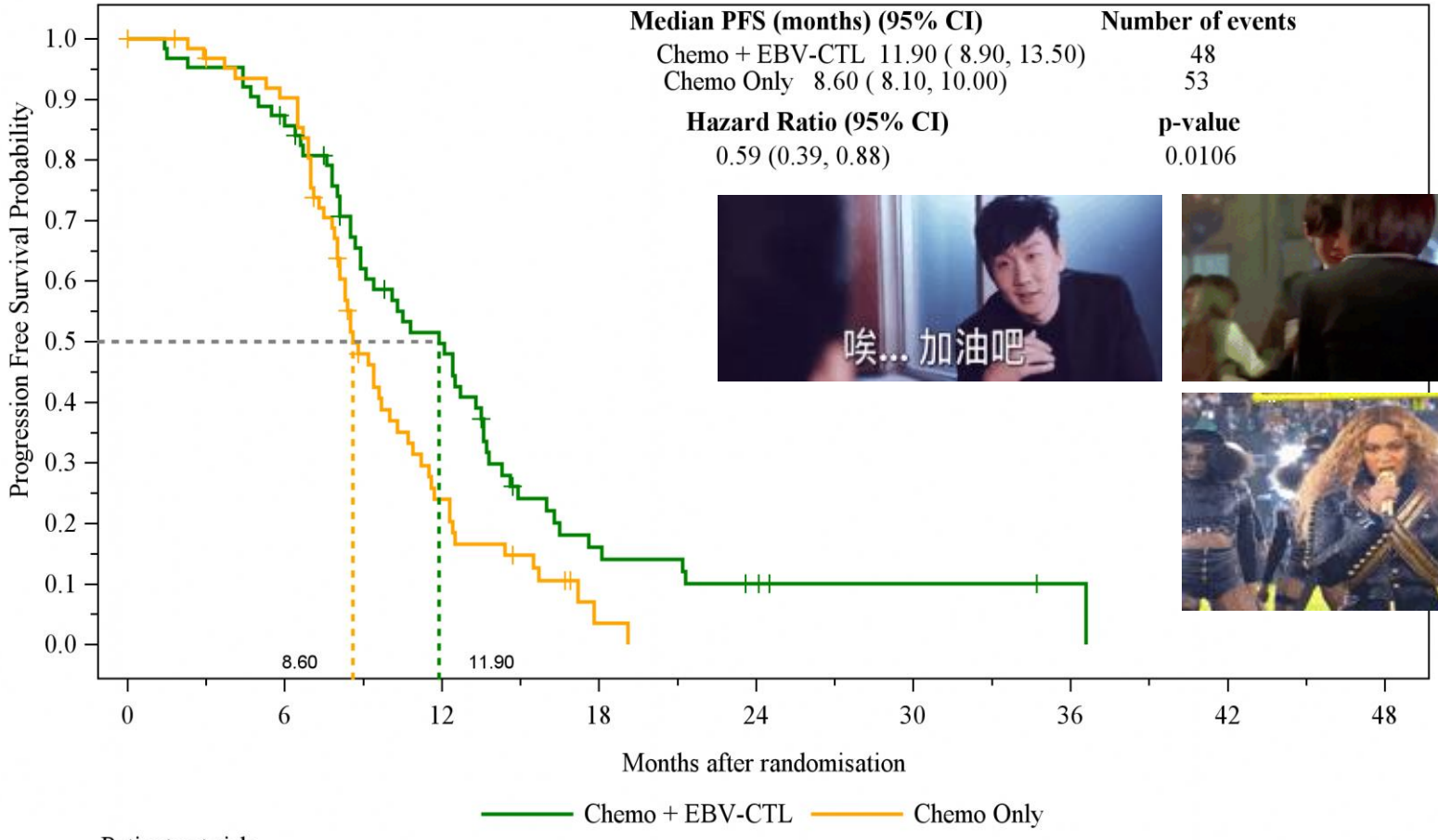


Progression-free Survival

Abbreviations: CI, confidence interval; EBV-CTL, Epstein Barr Virus-Specific Autologous Cytotoxic T Lymphocytes; NE, not evaluable; OS, overall survival; PFS, progression-free survival

Han Chong Toh

Figure 5.4.1 PFS: Kaplan-Meier Plot Progression Free Survival (PFS2) - (US, TW, and SG) - Intent to Treat Analysis Set

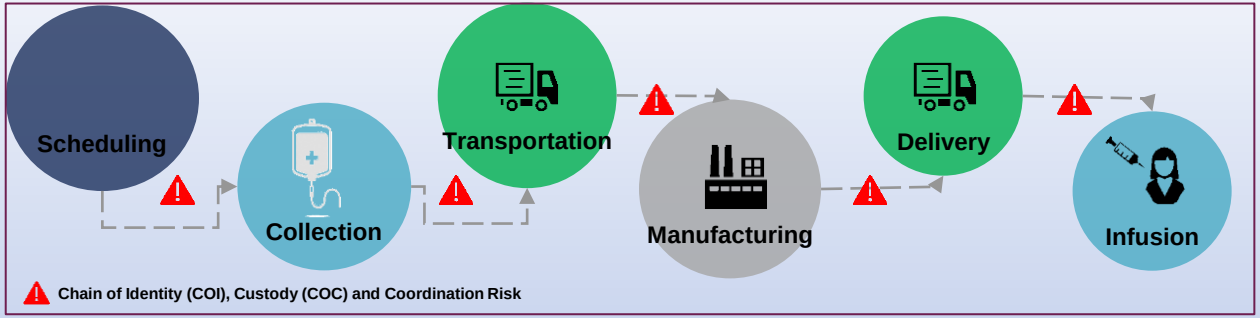


Patients at risk								
Chemo + EBV-CTL	65	54	28	8	4	2	1	0
Chemo Only	66	55	13	1	0			

Major Operations and Logistics : Over 3,000 Successful Shipments Through 79 Shipment Lanes Across 5 Countries

1. Scalable Logistics Network with Shipment Monitoring
2. **Manufacturing Scheduling**
3. **Chain-of-Identity, Chain-of-Custody**
4. Operations Support at Hospital Sites

Product Lifecycle / Logistic Step



Key Stake-holders	▪ Hospital Site Staff ▪ Courier ▪ Manufacturer	▪ Patient ▪ Hospital Site Staff ▪ Courier	▪ Hospital Site Staff ▪ Courier ▪ Manufacturer	▪ Patient ▪ Hospital Site Staff ▪ Manufacturer	▪ Hospital Site Staff ▪ Courier ▪ Manufacturer	▪ Patient ▪ Hospital Site Staff ▪ Courier ▪ Manufacturer
Coordination Elements	▪ Patient Appointment ▪ Blood draw and Shipment Scheduling ▪ Delivery Notification	▪ Clinical Site/Sample Collection Workflow ▪ Sample Collection Kits	▪ Shipment Tracking ▪ Proof of Delivery ▪ Temperature Records	▪ Manufacturing milestone updates ▪ Infusion Scheduling	▪ Shipment Tracking ▪ Proof of Delivery ▪ Temperature Records	▪ Patient Appointment ▪ Infusion Kits ▪ Infusion Workflow

PRODUCING A LOT OF EBV T CELLS

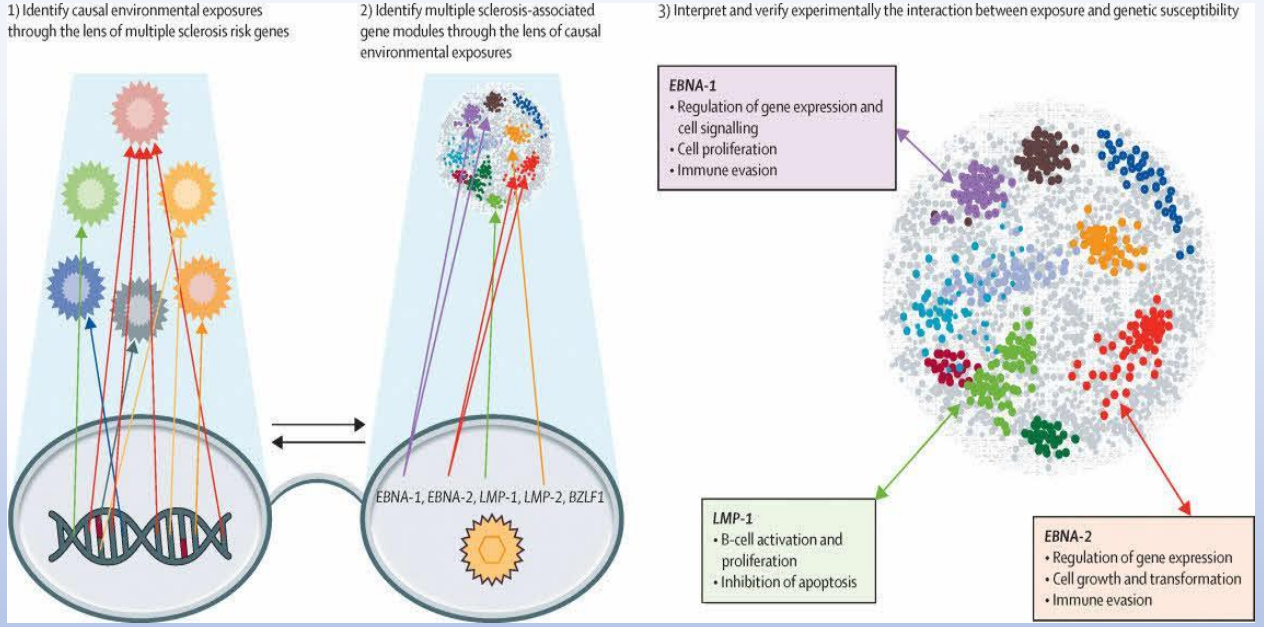
VANCE Trial Conclusions

- Global muticenter Phase III trial conducted across 5 countries
- Largest clinical trial of adoptive T cell therapy in solid tumors
- Evaluation of the efficacy and safety of gemcitabine and carboplatin followed by EBV-CTL versus gemcitabine and carboplatin alone as first line treatment for locally recurrent but incurable and metastatic NPC
- Central GMP facility – able to successfully produce sufficient EBV-CTL
- EBV-CTL treatment-well tolerated with a favorable safety profile
- No significant difference in OS between treatment arms
- Subgroup analysis showed a favorable OS of chemo + EBV-CTL arm in population of US, Taiwan and Singapore combined

Han Chong Toh

Abbreviations: EBV-CTL, Epstein Barr Virus-Specific Autologous Cytotoxic T Lymphocytes; NPC, nasopharyngeal carcinoma; OS, overall survival

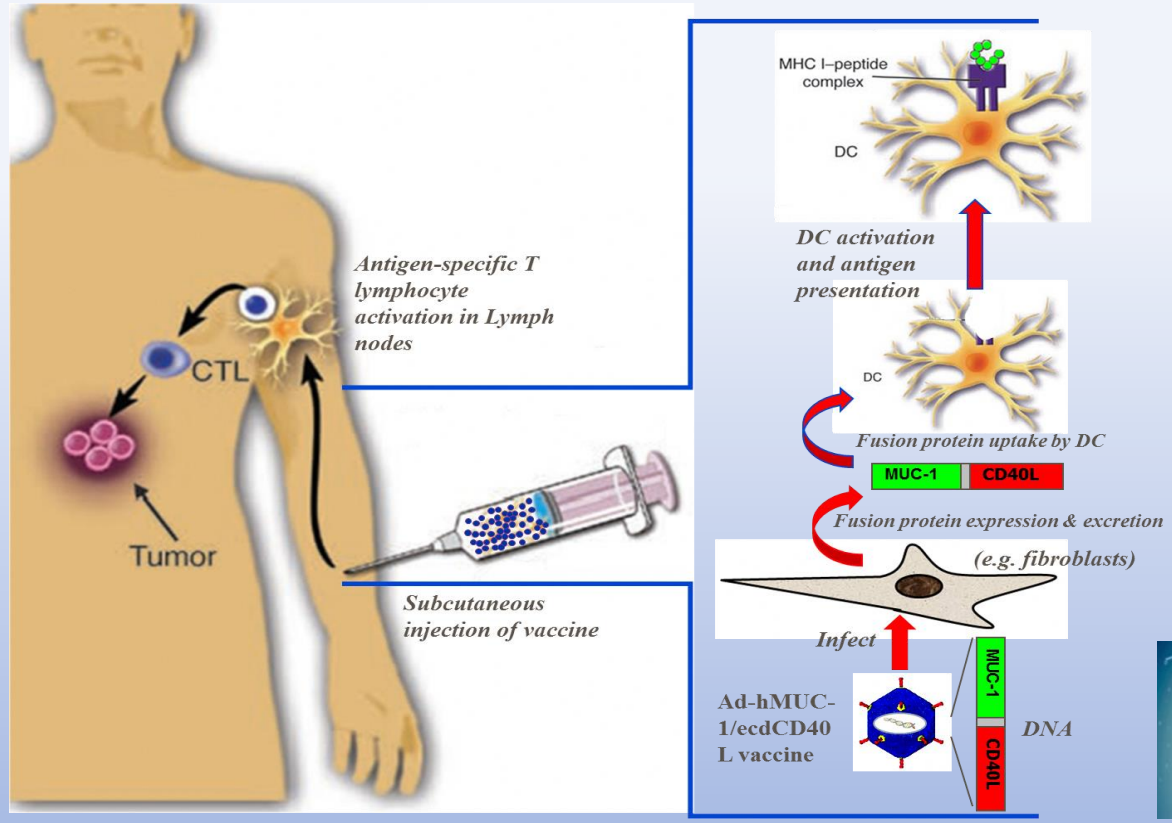
A NEW EBV RELATED ENTITY – MULTIPLE SCLEROSIS

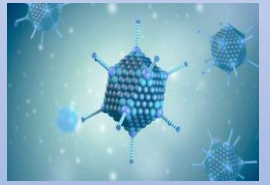


FIRST-IN-HUMAN CLINICAL TRIAL OF A MUC-1-CD40L VACCINE ON AN ADENOVIRUS BACKBONE

2014-2019

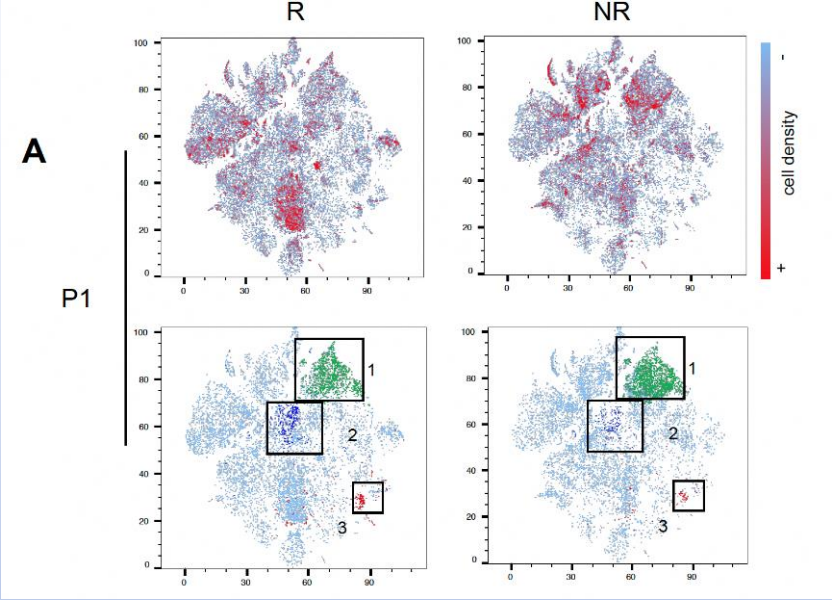
Targeting MUC-1 in epithelial cancers; Phase I n=21/24 (7 cohorts)

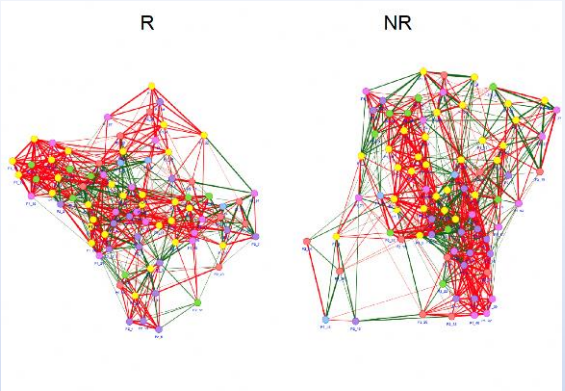


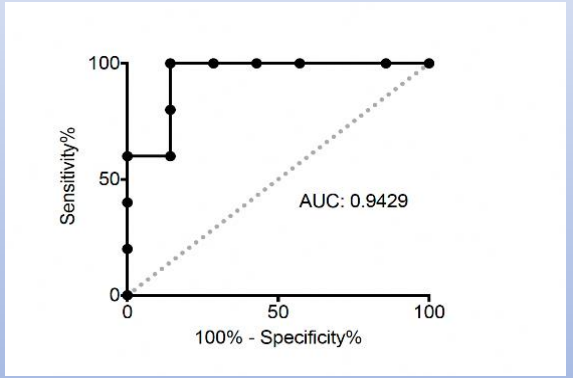


Nature Commun, Oct 2922

EPIC DISCRIMINATES AND PREDICTS RESPONDERS TO IMMUNOTHERAPY IN CANCER







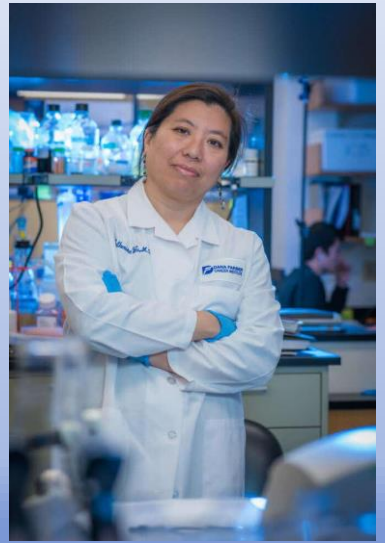
Elevation of GZMB+ CD8 T cells and B cells after vaccination in stable disease patients

Vaccination partially restored the connectivity of immune networks in cancer

Immune restoration was specifically present in a subset of patient cohort who had SD disease by RECIST

Nature Commun Oct 2022

The First Human Studies of Neoantigen Therapeutic Cancer Vaccines



A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells

Beatriz M. Carreno,[1*] Vincent Magrini,[2] Michelle Becker-Hapak,[1] Saghar Kaabinejadian,[3] Jasreet Hundal,[2] Allegra A. Petti,[2] Amy Ly,[2] Wen-Rong Lie,[4] William H. Hildebrand,[3] Elaine R. Mardis,[2] Gerald P. Linette[1]

› Nature. (Science 2015;348:803-808.)

Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer

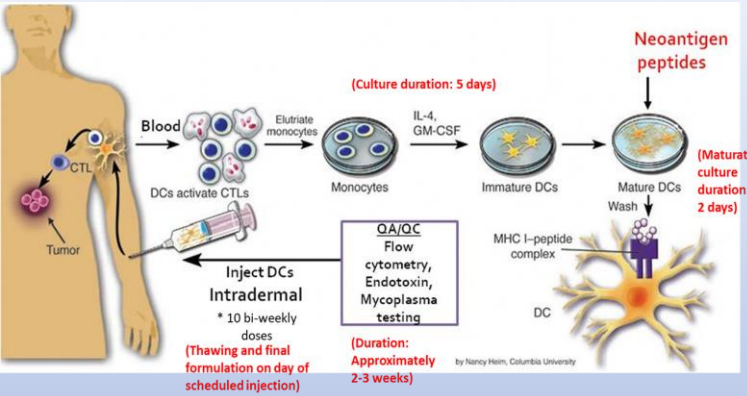
Ugur Sahin [1 2 3], Evelyna Derhovanessian [1], Matthias Miller [1], Björn-Philipp Kloke [1], Petra Simon [1], Martin Löwer [2], Valesca Bukur [1 2], Arbel D Tadmor [2], Ulrich Luxemburger [1], Barbara Schrörs [2], Tana Omokoko [1], Mathias Vormehr [1 3], Christian Albrecht [2], Anna Paruzynski [1],

Clinical Trial › Nature. 2017 Jul 13;547(7662):217-221. doi: 10.1038/nature22991. Epub 2017 Jul 5.

An immunogenic personal neoantigen vaccine for patients with melanoma

Patrick A Ott [1 2 3], Zhuting Hu [1], Derin B Keskin [1 3 4], Sachet A Shukla [1 4], Jing Sun [1], David J Bozym [1], Wandi Zhang [1], Adrienne Luoma [5], Anita Giobbie-Hurder [6], Lauren Peter [7 8], Christina Chen [1], Oriol Olive [1], Todd A Carter [4], Shuqiang Li [4], David J Lieb [4], Thomas Eisenhaure [4], Evisa Gjini [9], Jonathan Stevens [10], William J Lane [10], Indu Javeri [11], Kaliappanadar Nellaiappan [11], Andres M Salazar [12], Heather Daley [1], Michael Seaman [7], Elizabeth I Buchbinder [1 2 3], Charles H Yoon [3 13], Maegan Harden [4], Niall Lennon [4], Stacey Gabriel [4], Scott J Rodig [9 10], Dan H Barouch [3 7 8], Jon C Aster [3 10], Gad Getz [3 4 1], Kai Wucherpfennig [3 5], Donna Neuberg [6], Jerome Ritz [1 2 3], Eric S Lander [3 4], Edward F Fritsch [1 4], Nir Hacohen [3 4 1], Catherine J Wu [1 2 3 4]

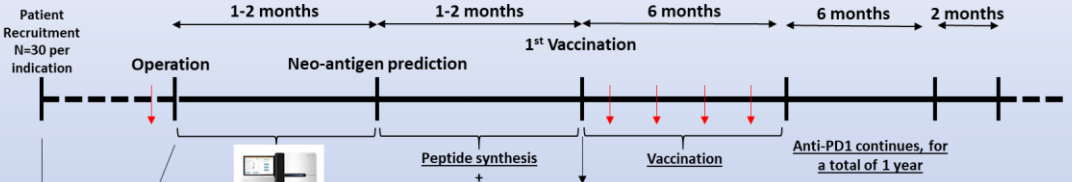
Open label, single-arm, Phase II Neoantigen Dendritic Cell vaccine and anti-PD1 (Nivolumab) as adjuvant treatment in resected hepatocellular carcinoma and liver metastases from colorectal cancer



Primary Liver Cancer/ Liver Metastasis Colorectal Cancer

Treatment Timeline

Clinical readout: 18-mth relapse free survival



Patient consent

Sample Collection: Tumour and adjacent non-tumour tissues

Next-generation Sequencing
- WES (somatic mutation)
- RNA-Seq (expressed mutation)
- HLA-typing

Neo-antigen prediction
Uni of Penn, Etcembly

Immunological readout: Blood sample collection. Including pre-operation, pre-. during, and post-vaccination blood samples.

Analytics

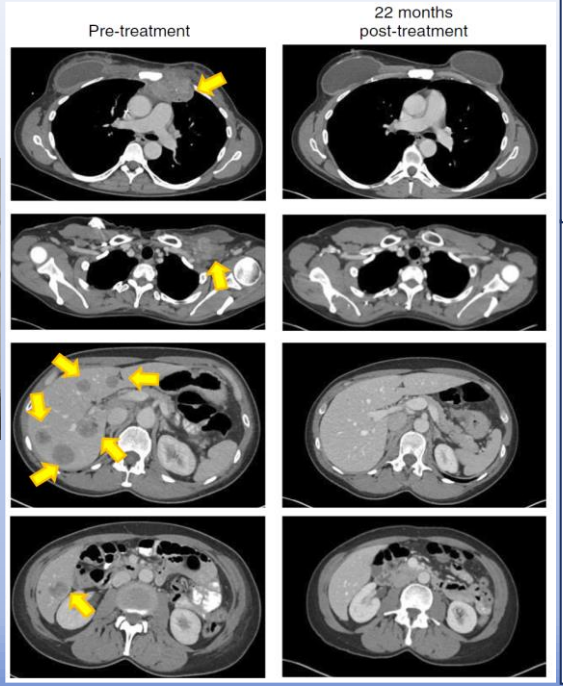
Immunomonitoring and Immunogram Analysis for Pre-, During, and Post-Vaccination Samples.

Identification and phenotypic analysis of antigen-specific T cells

-Information gathered will be critical for successful product/process development.

When Neoantigen targeting meets TIL

Neoantigen load predicted clinical benefit of adoptive T cell therapy.
Neoantigen-specific T cells are found among the TILs.
TIL products enriched for neoantigen specificity may possess enhanced efficacy.



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

Eric Tran, Ph.D., Paul F. Robbins, Ph.D., Yong-Chen Lu, Ph.D., Todd D. Prickett, Ph.D., Jared J. Gartner, M.Sc., Li Jia, M.Sc., Anna Pasetto, Ph.D., Zhili Zheng, Ph.D., Satyajit Ray, Ph.D., Eric M. Groh, M.D., Isaac R. Kriley, M.D., and Steven A. Rosenberg, M.D., Ph.D.

LETTERS
https://doi.org/10.1038/s41591-018-0040-8
nature medicine

Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer

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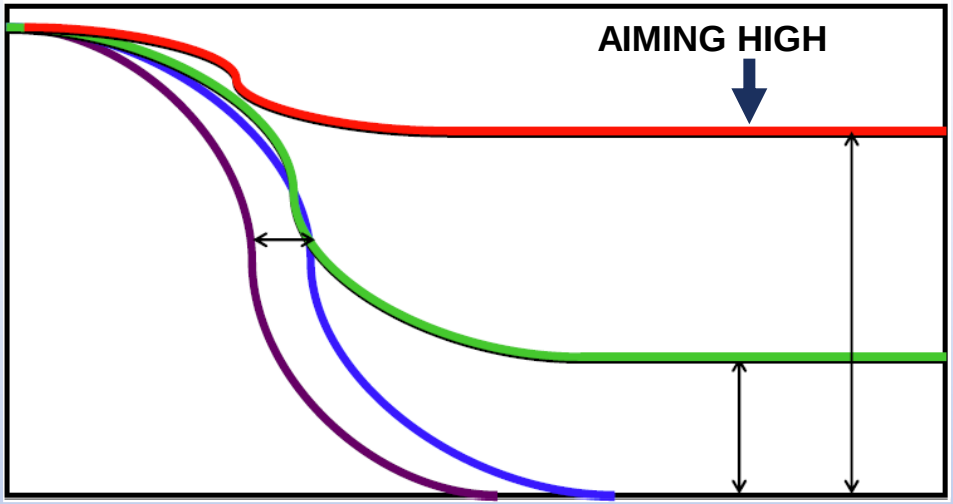
RISE OF IMMUNOTHERAPY COMBINATIONS WILL LEAD TO MORE SUPERSURVIVORS AND LIKELY MORE CURES



No Treatment

Immune Checkpoint Inhibitor

Standard Treatment

Combination Treatment

Only those who dare to fail greatly can ever achieve greatly.

(Robert Kennedy)

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THANK YOU

KEEP CALM AND BELIEVE IN SCIENCE